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10/777,470	02/11/2004	Abraham Phillip Lee	703538.4033	2234

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EXAMINER	
MUI, CHRISTINE T	

ART UNIT	PAPER NUMBER
1797	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/777,470	LEE ET AL.	
	Examiner	Art Unit	
	CHRISTINE T. MUI	1797	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,15-20 and 31-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11, 13, 15-20, 31-38 and 40-41* is/are rejected.

7)☒ Claim(s) *12 and 39* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

1. Applicant's arguments, see REMARKS, filed 06 October 2008, with respect to the rejection(s) of claim(s) 1-20 and 31-41 under 35 USC 102(b) and 35 UC 103(a) have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of Lee et al; USP 4,325,483 to Lombardo.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claim 17 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4. Claim 17 recites the limitation "flow rates" in line 1 of the instant claim . There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1-4, 15-16, 31-32 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee, Gwo-Bin et al (herein referred 'Lee') and further in view of USP 4,325,483 to Lombardo (herein referred 'Lombardo').

9. Regarding claims 1, 15-16, 31-32, the reference Lee discloses a novel micromachined chip of continuous multi-sample switching and injection for bio-analytical applications. As seen in Figure 5, there is schematic representation of hydrodynamic focusing where there is three inlets into the device where the first stream is the sample stream of a first solution which is sandwiched between the second and third streams

comprising of a sheath flow (see Figure 5, Section 4). Lee does not disclose forming a droplet from the first stream by controlling the shear forces.

10. Lombardo discloses a method for detecting and controlling the flow rate of a perturbed, droplet-forming stream. The fluid flow rate is increased or decreased to droplet formed from a flow means of a continuous particle containing stream and a surrounding sheath stream. The stream is caused to form discrete droplet under influence of perturbation with at least a preselected frequency and amplitude. Once the droplet is formed from the sample stream surrounded by the sheath stream, surface characteristics of the droplet are analyzed by a sheath sensing means and particle detecting means and compared to the desired characteristics and the fluid flow rate is increased or decreased to generate a more desired droplet. As seen in Figure 1, a laminar stream of the continuous and sheath stream pass by a particle detector point at which incident radiant energy form a particle detector souse facilitates detection of the a particle to be sorted by particle detector receptors (see abstract, column 7, lines 8-47, column 8, lines 21-40). It is interpreted by the examiner that the increase or decrease of the fluid flow rate of the sheath stream to change the droplet characteristics is considered to change the shear forces upon the sample stream. It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the velocities of the streams of Lee as it is modified in Lombardo to generate desired droplet characteristics so that one can either compare and analyze the droplet to the desired characteristics or to change the flow rates to generate a droplet of a new size or composition.

11. Regarding claim 2, the references Lee and Lombardo disclose the claimed invention. Lombardo discloses a continuous particle continuing stream with a surrounding sheath stream (see column 7, lines 8-15). It is interpreted by the examiner that since sheath stream only surrounds the continuing stream, this is considered to be two immiscible stream where one stream does not diffuse into the other. It would have been obvious to one having ordinary skill in the art at the time the invention was made to generate a droplet with two immiscible streams that one stream surrounds or encompasses the other stream neglecting a mixing and diffusion between the streams as a droplet and creating layers.

12. Regarding claims 3-4, the references Lee and Lombardo disclose the claimed invention. Lee discloses the micromachined chip as seen in Figure 5 with three stream, where a sample stream is sandwiched between two sheath streams. As seen in the figure and in Formula (2) each channel has its own velocity and density of the fluid in the channel, as well as its own diameter (see Figure 5, Section 4). This is interpreted by the examiner, that is a matter of design choice depending on the intended use of the device that three stream may be the same or different. It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the contents of the inlet stream as this is a matter of design choice to be solutions that are mentioned in the instant claim to create a droplet of desired contents and size, depending on the density of the fluid and the velocity the fluid is going through the channels.

13. Regarding claim 38, the reference Lee discloses a novel micromachined chip of continuous multi-sample switching and injection for bio-analytical applications. As seen in Figure 5, there is schematic representation of hydrodynamic focusing where there is three inlets into the device where the first stream is the sample stream of a first solution which is sandwiched between the second and third streams comprising of a sheath flow. The three inlet channels flow into an output channel as seen in the Figure 5. As seen in another embodiment of the micomachined chip, Figure 6, multiple channel inlets are filled with fluids, each by a syringe pump (see Figure 5 and 6, Section 4). It is interpreted by the examiner that each of the sheath and sample flow channels are supply by fluid with a syringe pump as in Figure 6, since it is indicted that each of the channels may have fluid flow through the channel with a different velocity. Lee does not disclose forming a droplet from the first stream by controlling the shear forces. Lombardo discloses a method for detecting and controlling the flow rate of a perturbed, droplet-forming stream. The fluid flow rate is increased or decreased to droplet formed from a flow means of a continuous particle containing stream and a surrounding sheath stream. The stream is caused to form discrete droplet under influence of perturbation with at least a preselected frequency and amplitude. Once the droplet is formed from the sample stream surrounded by the sheath stream, surface characteristics of the droplet are analyzed by a sheath sensing means and particle detecting means and compared to the desired characteristics and the fluid flow rate is increased or decreased to generate a more desired droplet. As seen in Figure 1, a laminar stream of the continuous and sheath stream pass by a particle detector point at which incident radiant

energy form a particle detector souse facilitates detection of the a particle to be sorted by particle detector receptors (see abstract, column 7, lines 8-47, column 8, lines 21-40). It is interpreted by the examiner that the increase or decrease of the fluid flow rate of the sheath stream to change the droplet characteristics is considered to change the shear forces upon the sample stream. It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the velocities of the streams of Lee as it is modified in Lombardo to generate desired droplet characteristics so that one can either compare and analyze the droplet to the desired characteristics or to change the flow rates to generate a droplet of a new size or composition.

14. Claims 5-7, 13 and 17-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee and Lombardo as applied to claim 1, and further in view of CA 2 304 644 to Klinksiek et al (herein referred Klinksiek).

15. CA 2 304 644 has the publication date of April 1999 is also published as DE 198 14 267 published March 1998 and WO 99/15263 published April 1998. The basis of the rejection is made off of the English Translation of WO 99/15263.

16. Regarding claim 5, the reference Lee and Lombardo disclose the claimed invention except for dissolving a reagent in the first solution. Klinksiek discloses a device for the preparation of a silicone, silane or silicone/silane emulsion composed of a silicone containing and/or silane-containing active substance component and an aqueous phase. Furthermore, Klinksiek discloses that it is known in the art to prepare a fine particle and stable silicone emulsion of oil in water. Prior to homogenization, silicon is introduced slowly with stirring into an aqueous emulsifier mixture before the resulting

coarse-particle emulsion undergoes actual homogenization (see page 1, lines 3-5 and 12-14, page 4, lines 16-23 and 29-30). It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify first solution by adding a reagent to the first solution to alter to content of the droplet to a desired concentration or characteristic.

17. Regarding claim 6, the references Lee and Lombardo disclose the claimed invention except for adding a reagent such as a drug. Klinksiek discloses dissolving a reagent to a first solution, but does not specifically disclose adding reagent comprising a drug. Klinksiek teaches that it is known in the art to slowly stir in silicon particles into an aqueous solution (see page 1, lines 12-14). It would have been obvious to one having ordinary skill in the art at the time the invention was made to add a drug reagent instead of silicon particles to the aqueous solution to produce microparticles with a drug rather than silicone and add a drug to the droplet formed for a desired content or characteristic.

18. Regarding claims 7 and 13, the references Lee and Lombardo disclose the claimed invention except for the type of molecules in the second solution. Klinksiek discloses adding in particles to the aqueous solution, but does not disclose amphiphilic molecules in the second solution. Klinksiek discloses that the aqueous phase may contain an emulsifier that contains silicon active substances. The amount of emulsifier may be modified in such a way that operations are carried out with any deficient amount of water that may contain the entire quantity of emulsifier (see page 6, line 28-page 7, line 19). It is interpreted by the examiner that the emulsifier is a type of amphiphilic

molecule in an aqueous solution. It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the content of the aqueous phase by adding an emulsifier that displays both hydrophobic and hydrophilic properties.

19. Regarding claims 17-20, the references Lee, Lombardo and Klinksiek disclose the claimed invention. Lee discloses the three inlet channels flow into an output channel as seen in the Figure 5. As seen in another embodiment of the micomachined chip, Figure 6, multiple channel inlets are filled with fluids, each by a syringe pump (see Figure 5 and 6, Section 4). It is interpreted by the examiner that each of the sheath and sample flow channels are supply by fluid with a syringe pump as in Figure 6, since it is indicted that each of the channels may have fluid flow through the channel with a different velocity. Lombardo discloses a method for detecting and controlling the flow rate of a perturbed, droplet-forming stream. The fluid flow rate is increased or decreased to droplet formed from a flow means of a continuous particle containing stream and a surrounding sheath stream. Once the droplet is formed from the sample stream surrounded by the sheath stream, surface characteristics of the droplet are analyzed by a sheath sensing means and particle detecting means and compared to the desired characteristics and the fluid flow rate is increased or decreased to generate a more desired droplet. As seen in Figure 1, a laminar stream of the continuous and sheath stream pass by a particle detector point at which incident radiant energy form a particle detector souse facilitates detection of the a particle to be sorted by particle detector receptors (see abstract, column 7, lines 8-47, column 8, lines 21-40).

20. Neither Lee nor Lombardo discloses the contents of the sample and sheath stream, but It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the contents of the inlet stream as this is a matter of design choice to be solutions that are mentioned in the instant claim to create a droplet of desired contents and size, depending on the density of the fluid and the velocity the fluid is going through the channels.

21. It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the velocities of the streams of Lee as it is modified in Lombardo to generate desired droplet characteristics so that one can either compare and analyze the droplet to the desired characteristics or to change the flow rates to generate a droplet of a new size or composition.

22. Claims 8-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee and Lombardo in view of Klinksiek as applied to claim 1, and further in view of Handa et al. (herein referred "Handa").

23. Regarding claims 8-9, the references Lee, Lombardo and Klinksiek disclose the claimed invention except for producing a mono- and bi- layer vesicle with an amphiphilic molecule. Handa discloses a method for producing a phospholipid monolayer at the triolein saline interface that is converted into a bilayer through differential quenching of N-dansyl-PE (see abstract and page 2888, left column, Formation of Microemulsion). It would have been obvious to one having ordinary skill in that art at the time the invention was made to produce a monolayer vesicle and convert it into a bilayer vesicle in order

to determine the stability of the monolayer and to examine the properties of the bilayer in the pharmaceutical, chemical or medicine fields.

24. Regarding claims 10-11, the references Lee, Lombardo and Klinksiek disclose the claimed invention except for using different types of amphiphilic molecules in the production of the vesicles. Handa discloses that in experimentation, the interfacial tensions of phospholipids include phosphatidylcholine, phosphatidylethanolamine and phosphatidylserine, in the triolein saline emulsion (see abstract). It would have been obvious to one having ordinary skill in that art at the time the invention was made to examine different amphiphilic molecules to determine the stability and interfacial tension of the monolayers of each lipid for purposes of testing in pharmaceutical, chemicals or medicines.

25. Claims 33 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee and Lombardo as applied to claims 32 and 38 respectively, and further in view of USP 6,211,654 to Quake (herein referred "Quake").

26. Regarding claims 33 and 40, the references Lee and Lombardo disclose the claimed invention except for a droplet sorter. Quake discloses a microfabricated device that analyzes and sorts single polynucleotides by size. The device has a solution inlet that has a plurality of branch channels that are in fluid communication and branch out from the discrimination region. The flow of molecules is maintained through the device via a pump of pressure differential and a directing means comprising of a valve structure at the branch point effective to permit the molecule to enter only one of the branches (see column 2, lines 49-51, 63-67, column 7, line 8, 14-20 and Figure 1). It

would have been obvious to one having ordinary skill in that art at the time the invention was made to sort the droplets that are formed via an input channel and a daughter channel from the laminar stream of Lombardo once the sheath and continuing particles have formed a droplet of desired characteristics that are regulated via pumps to maintain a flow and a pressure gradient to avoid the droplets in the device from being stagnant and move through the device without the risk of the droplets merging into a larger droplet.

27. Claims 34-37 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee and Lombardo as applied to claims 31 and 38 respectively, and further in view of USP 6,733,172 to Lee (herein referred "Lee II").

28. Regarding claims 34-36, the references Lee and Lombardo disclose the claimed invention except for splitting the formed droplet. Lee II discloses a magnetohydrodynamic fluidic system that splits droplets in a MHD microfluidic channel (see column 5, lines 65-66). An initial droplet in the droplet splitter channel is moved along the microfluidic channel by utilizing a sequential set of MHD pumps. The pumps provide a MHD micropump in which the Lorentz force is used to propel the droplet along the microchannel. The droplet is stretched into separate droplets by control of the MHD pumps that are selectively activated to stretch the droplet until the components are separate (see column 6, lines 1-6 and 21-31). Since the controls are selectively activated the droplet splitter is capable of producing equal and unequal sized droplets by activating particular pumps to stretch and separate the components. It would have

been obvious to one having ordinary skill in the art at the time the invention was made to split a droplet into smaller components for minuscule sampling or testing of droplets.

29. Regarding claims 37 and 41, the references Lee and Lombardo disclose the claimed invention except for a droplet fuser. Lee II discloses a magnetohydrodynamic fluidic system that mixes droplets. The droplet mixer disclosed is enhanced by stretching one droplet to engulf another. A first droplet is introduced into a microchannel and moved along the channel by a set a MHD pumps and stretched into two separate component sections. A second droplet is introduced into another microchannel and moved toward the first stretched droplet by use of the MHD pumps and moved into contact with the first droplet between the two separate component sections of the droplet. The set of MHD pumps are used to combine the droplet to form a mixed material (see column 6, lines 43-56; Figures 3A-B). It would have been obvious to one having ordinary skill in the art at the time the invention was made to fuse together two microparticles in a device to form a larger particle with either different or identical concentrations to produce a well-mixed particle for analysis.

Allowable Subject Matter

30. Claims 12 and 39 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

31. A method for generating droplets from three inlet streams, where the first stream comprise a first solution and the second and third stream comprise a second solution forms an interface flowing through two downstream input channels is not found, taught

nor suggest in the prior art. The limitation of two downstream input channels is not found obvious over the closest prior art of Figure 5 of Lee.

32. Furthermore, the microfluidic channel where the droplet process comprises of at least two daughter channels in communication with the splitter channel is not found, taught or found obvious over the prior art. The closes prior art of Thorsen splits the droplet, but splits the droplet, but combines to form one daughter channel.

Conclusion

33. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Lee, Gwo-Bin et al., Hydrodynamic Focusing for a Micromachined Flow Cytometer, 2001, Journal of Fluids Engineer, 123, 672-679.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRISTINE T. MUI whose telephone number is (571)270-3243. The examiner can normally be reached on Monday-Thursday 7-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Walter Griffin can be reached on (571) 272-1447. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

CTM

/Jill Warden/
Supervisory Patent Examiner, Art Unit 1797